# Limitations in Biexponential Fitting of Nuclear Magnetic Resonance (NMR) Inversion-Recovery Data to Differentiate Between Cell Compartmental NMR Signals

Mohammed Salman Shazeeb[1,2]

[1]*Radiology, University of Massachusetts Medical School, Worcester, MA, United States,* [2]*Biomedical Engineering, Worcester Polytechnic Institute, Worcester, MA, United States*

**Introduction:** The apparent diffusion coefficient (ADC) of cerebral tissue water is known to decrease during the early stages of ischemia, but it is unclear whether these changes occur in the intracellular (IC) space, extracellular (EC) space, or both. Past studies have measured compartment-specific diffusion coefficients using gadolinium (Gd-DTPA) as an EC contrast agent, thereby reducing the longitudinal ($T_1$) relaxation time constant (RTC) of the EC water signal [1]. Alternatively, IC contrast agents like manganese ($Mn^{2+}$) can be used to shorten the $T_1$ RTC of the IC water signal where $Mn^{2+}$ enters the cells via calcium channels [2]. The relative difference in $T_1$ RTCs between the IC and EC compartmental signals can be used to discriminate between MR signals arising from water in the respective compartments. In either case, a biexponential model can be used to fit inversion-recovery (IR) NMR data using non-linear least-squares fit to calculate the RTCs and relative water magnetization fractions (MagFs) of the compartmental signals using Eq.{1}, where $M_z$ is the signal intensity, $TI$ is the inversion time, $\beta$ is the efficiency of inversion (ideally~2), $M_{0a}$ and $M_{0b}$ correspond to the apparent water signals, and $T_{1a}$ and $T_{1b}$ are the apparent longitudinal RTCs of the respective compartmental signals. Due to the presence of noise and sensitivity to actual observed parameter values, the fitted parameters display different amounts of error depending on whether an EC or IC contrast agent is administered. Silva *et al.* looked at the effects of signal-to-noise ratio (SNR) and parametric limitations on biexponential fitting using the IR model assuming the contrast agent to reside in the EC compartment [3]. In this study, we report a comprehensive error analysis of noise effects and parametric limitations using simulated IR data by extending to scenarios where the contrast agent can reside in IC, EC, or even both compartments.

$$M_z(TI) = M_{0a}\cdot\left(1-\beta\cdot e^{-\frac{TI}{T_{1a}}}\right) + M_{0b}\cdot\left(1-\beta\cdot e^{-\frac{TI}{T_{1b}}}\right) \qquad \{1\}$$

$$RMSPE = 100\%\cdot\sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\frac{x_i-\mu_i}{\mu_i}\right)^2} \qquad \{2\}$$

**Methods:** MATLAB was used to generate simulated IR data sets with 16 $TI$ values sampled logarithmically using Eq. {1}. Five different ratios were calculated for $T_{1a}$:$T_{1b}$ (1:2, 1:4, 1:6, 1:8, and 1:10) and $M_{0a}$:$M_{0b}$ (1:1, 1:2, 1:3, 1:5, and 1:10) generating a total of 25 data sets with all possible combinations which account for the association of the smaller MagF with the smaller RTC and the larger MagF with the larger RTC ("*match*" data sets). Separate IR data sets were generated by reversing the assignment of the RTCs and the MagFs to accommodate for the scenario where the contrast agent resides in the IC compartment generating 25 additional data sets with all possible combinations ("*cross-match*" data sets). The combination of these ratios were selected to span a wide range of exchange regimes for the system varying from fast to intermediate to slow with the contrast agent residing in the IC or EC compartment. The lowest $T_{1a}$ (75 ms) and highest $T_{1b}$ (750 ms) were chosen based on RTCs observed in previous experiments [1,3]. Gaussian noise was added to the simulated data sets to assess the robustness of the biexponential fitting model and accuracy of the fit parameters. One hundred test data sets were generated for each of the 50 simulated IR data sets (*match* and *cross-match*) with the following SNRs: 10, 25, 50, 100, and 150. For all generated data sets (total of 25,000), the five parameters from Eq. {1} were fitted using the 'Trust Region' nonlinear least squares algorithm in MATLAB. Root mean square percentage error (RMSPE) was calculated using Eq. {2}, where $N$ = 100, $x_i$ is the calculated parameter value, and $\mu_i$ is the actual parameter value. Accuracy of the fits as a function of SNR was determined by taking a sum of the RMSPE of the simulated *match* and *cross-match* IR data sets at a given SNR.

**Results and Discussion:** Previous works have explored the accuracy of two component fits of a simple biexponential decay model using different statistical methods [4-6]. However, quantification of errors associated with each of the fitted parameters using the IR model is still unexplored. In Fig. 1, the general trend indicates that for *match* data sets the error in fitting $M_{0a}$ and $T_{1a}$ increased to an RMSPE of ~100% and ~12%, respectively, as the RTCs became more similar and the MagFs more dissimilar. A different outcome resulted for *cross-match* data sets: the error in fitting $M_{0a}$ and $T_{1a}$ increased to an RMSPE of ~10% and ~3%, respectively, as both the RTCs and MagFs became more similar. For both *match* and *cross-match* data sets, the error in fitting $M_{0b}$ and $T_{1b}$ increased as the RTCs became more similar at all MagF scenarios. However, the error was the highest when the MagFs were dissimilar and the RTCs approached similarity: *match* data sets had an RMSPE of ~9% and ~250% and *cross-match* data sets had an RMSPE of ~10% and ~200% for $M_{0b}$ and $T_{1b}$, respectively. The error in fitting the pre-exponential multiplier $\beta$ was similar for all data sets (<0.2%). Tables 1 and 2 show that for both data sets, the RMSPE sum error of each parameter decreased with increasing SNR. The *cross-match* data sets showed ~10 times less error for $M_{0a}$ and ~5 times less error for $T_{1a}$ compared to the *match* data sets. The remaining three parameters ($M_{0b}$, $T_{1b}$, and $\beta$) showed relatively little difference in errors between the two data sets.

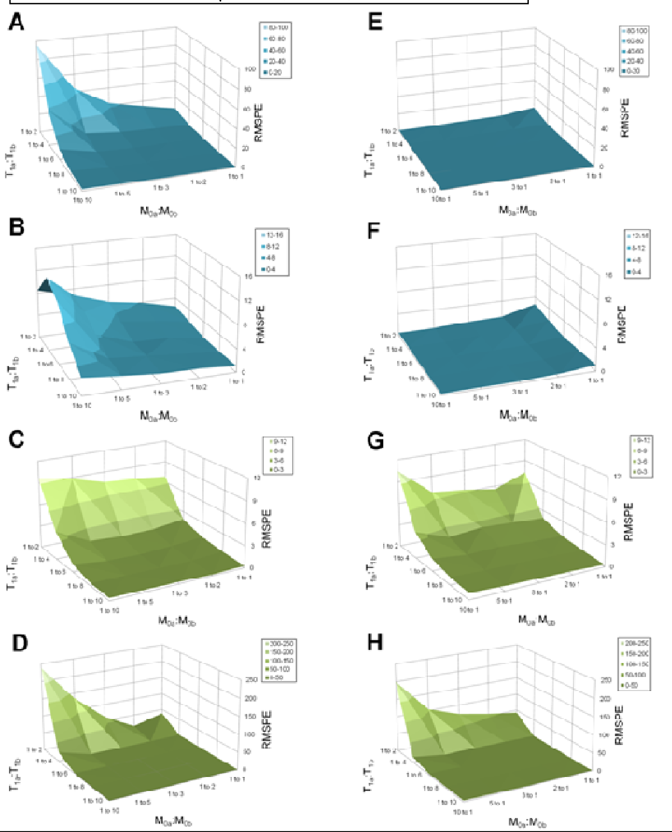

**Fig. 1** – 3D surface plots of RMSPE for the fitted values of $M_{0a}$ (**A**, **E**), $T_{1a}$ (**B**, **F**), $M_{0b}$ (**C**, **G**) and $T_{1b}$ (**D**, **H**) for different ratio combinations of actual $M_{0a}$:$M_{0b}$ and $T_{1a}$:$T_{1b}$ values at an SNR value of 50. The RMSPE data on the left column (**A–D**) corresponds to the *match* data sets while the RMSPE data on the right column (**E–H**) corresponds to the *cross-match* data sets.

| | SNR | | | | |
|---|---|---|---|---|---|
| | **10** | **25** | **50** | **100** | **150** |
| $M_{0a}$ | 685.8 | 479.4 | 267.8 | 160.5 | 72.3 |
| $M_{0b}$ | 137.6 | 91.6 | 56.3 | 33.1 | 14.6 |
| $T_{1a}$ | 478.2 | 226.8 | 96.6 | 42.6 | 18.6 |
| $T_{1b}$ | 2834.8 | 1364.6 | 529.2 | 130.2 | 7.4 |
| $\beta$ | 13.7 | 4.8 | 2.1 | 0.8 | 0.3 |

Table 1. RMSPE sum of calculated parameters from *match* data sets at different SNR values.

| | SNR | | | | |
|---|---|---|---|---|---|
| | **10** | **25** | **50** | **100** | **150** |
| $M_{0a}$ | 63.7 | 36.8 | 24.7 | 14.0 | 6.6 |
| $M_{0b}$ | 132.6 | 88.3 | 61.4 | 37.3 | 18.5 |
| $T_{1a}$ | 74.6 | 28.8 | 17.3 | 8.7 | 3.8 |
| $T_{1b}$ | 2676.7 | 1177.1 | 525.3 | 90.4 | 13.4 |
| $\beta$ | 11.5 | 4.5 | 2.1 | 0.9 | 0.4 |

Table 2. RMSPE sum of calculated parameters from *cross-match* data sets at different SNR values.

**Conclusion:** We explored variations of RTC and MagF ratios and quantified the errors in the fitted parameters using RMSPE and demonstrated that *match* and *cross-match* data sets generate different amounts of error due to the constraints of fitting. This error analysis should enable more precise relaxography and diffusion measurements by identifying whether the calculated fitted values are over or underestimations of the true apparent values in Eq. {1}.

**References:** [1] Silva *et al.* (2002). Magn Reson Med **48**:826-37; [2] Lin *et al.* (1997). Magn Reson Med **38**:378-88; [3] Silva *et al.* (1998). IEEE 24th Ann Northeast Bioeng Conf pp:35-37. [4] Istratov *et al.* (1999). Rev Sci Instrum **70**:1233-57. [5] Kroeker *et al.* (1986). J Magn Reson **69**:218-35; [6] Bretthorst *et al.* (2005).